Remarks

Amendments to the Claims

Claims 1 and 10 were amended to incorporate the limitations of claims 4 and 12, now limited to gel; claims 1 and 10 were also amended to limit the drugs to those in claims 6 and 13, amended to define a more narrow group, specifically, danazol, bromocriptine, and luteinizing hormone-releasing hormone (LHRH) analogues; and claims 1 and 10 were amended to define the drug amount as regionally effective and in a dosage that provides regionally and not systemically effective levels, and claim 18 cancelled. Claim 5 is now dependent on claim 3. Claims 8 and 15 now depend on claims 3 and 11, respectively.

Rejection Under 35 U.S.C. § 112,enablement and definiteness

Claims 1-5 were rejected under 35 U.S.C. § 112, first paragraph, as non-enabled. Applicants respectfully traverse this rejection, although the issue is now moot in view of the amendment to the claims to incorporate the drugs of claim 6 into the independent claims.

Claims 1-8 were rejected under 35 U.S.C. § 112, second paragraph, as indefinite in view of the negative exclusion of the independent claim. Applicants respectfully traverse this rejection, although the issue is now moot in view of the removal of the phrase from the independent claims.

Rejection Under 35 U.S.C. §102

Claims 1, 2, and 4-7 were rejected under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 4,919,937 to Mauvais-Jarvis, *et al.* ("Jarvis") as evidenced by U. S. Patent No. 5,580,857 to Oden ("Oden"). Applicants respectfully traverse this rejection.

Mauvais-Jarvis

Mauvais Jarvis discloses an anti-estrogen drug which is derived from tamoxifen, for treament of breast cancer. The drug can be administered in an aqueous alcoholic gel to the breast. The examiner's attention is drawn to col. 2, lines 51-54, which clearly states that the drug passes through the skin in the absence of a penetration enhancer. Therefore, one would question why one would add a penetration enhancer to the formulation Applicants agree with the Examiner that Oden discloses triethanolamine as an Example of a penetration enhancer. However, triethanolamine has many applications; for example, triethanolamine is commonly used in formulations as a ph adjuster/modifying agent (see for example U. S. Patent No. 6,730,323 to Murley et al. at col. 2, lines 20-35 and U.S. Patent No. 5,976,566 to Samour, et al., col. 6, line 46) and also, and as an emulsifier. Applicants are unclear as to the Examiner's reason for concluding that triethanolamine is employed as a penetration enhancer in Jarvis, considering the statements that indicate no penetration enhancer is required. Studies by Gwak and Chun, *Int. J. Pharm.*, 236:57-64 (2002) ("Gwak") a copy of which was perviously submitted) show that triethanolamine at concentrations of 1% does not have penetration enhancing effects (Jarvis discloses a formulation containing about 1-1.5% triethanolamine). Thus, a disclosure of triethanolamine is not tantamount to the disclosure of a penetration enhancer. Jarvis is silent about the use of a penetration enhancer. A reference is considered as a whole, and there is nothing in Jarvis that would lead one of ordinary skill in that art to conclude that triethanolamine is used as a penetration enhancer or what concentration of triethanolamine would promote

delivery of a drug across the stratum corneum; as discussed above, the concentration of triethanolamine disclosed in Jarvis are not effective to enhance penetration (see Gwak).

However, this rejection is moot in view of the limitation of the independent claims to define the drug danazol, bromocriptine, or luteinizing hormone-releasing hormone (LHRH) analogues. Mauvais Jarvis does not disclose any of these drugs.

Rejection Under 35 U.S.C. § 103

Claims 1-4 and 6-8 were rejected under 35 U.S.C. § 103(a) as unpatentable over U.S. Patent No. 5,993,856 to Ragavan, et al. ("Ragavan 1"). Applicants respectfully traverse this rejection.

Legal Standard

Obviousness is a legal conclusion based on underlying facts of four general types, all of which must be considered by the examiner: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) any objective indicia of nonobviousness. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 148 U.S.P.Q. 459 (1966). The *Graham* analysis was recently affirmed on April 30, 2007 by the Supreme Court in *KSR Int'l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 82 U.S.P.Q.2d 1385 (2007). The Court recognized that a showing of "teaching, suggestion, or motivation " to combine the prior art to meet the claimed subject matter could provide a helpful insight in determining whether the claimed subject matter is obvious under 35 U.S.C. § 103(a).

The obviousness analysis requires looking at the invention as a whole. "Focusing on the obviousness of substitutions and differences, instead of on the invention as a whole, is a legally

improper way to simplify the often difficult determination of obviousness." *Gillette Co. v. S.C. Johnson & Sons, Inc.*, 919 F.2d 720, 724, 16 U.S.P.Q.2d 1923 (Fed. Cir. 1990); *see Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1383, 231 U.S.P.Q. 81, 93 (Fed. Cir. 1986).

Hindsight analysis, such as picking and choosing from prior art references using the claimed invention as a template, has long been forbidden. *See e.g. In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988), stating "One cannot use hindsight reconstruction to pick and choose among isolated disclosures on the prior art to deprecate the claimed invention." In *KSR*, the Court also warned against the use of hindsight analysis in making an obviousness determination. The Court stated, "A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning." (*KSR*, 127 S. Ct. at 1742, citing *Graham*, 383 U.S. at 36 (warning against a "temptation to read into the prior art the teachings of the invention in issue" and instructing courts to "guard against slipping into the use of hindsight" (quoting M*onroe Auto Equipment Co. v. Heckethorn Mfg. & Supply Co.*, 332 F.2d 406, 412, 141 U.S.P.Q. 549 (6th Cir. 1964)).

Analysis

The scope and contents of the prior art

Ragavan 1

Ragaven 1 discloses formulations for topical or local delivery for administration of drugs to a region such as the *reproductive organ* and the surrounding environs (Ragavan 1, col. 7, lines 37-40). Although Ragavan 1 discloses including standard excipients in the formulation (*See* col. 3, line 24-37), Ragavan 1 is silent about including penetration enhancers in the formulation. The

formulations disclosed in Ragavan 1 comprise an effective amount of a drug for treating a region. "Region" is defined in Ragavan 1 as reproductive organs and their surrounding environs, which include uterus, fallopian tube, peritoneal space, pelvic cul-de-sac, ovaries, perineum and the rectovaginal region (*See* Ragavan 1, at least at col. 7, lines 37-41). Thus, formulations disclosed in Ragavan 1 are meant for delivery across *mucosal membranes*, which does not present anywhere near the difficulty with respect to drug transport, into a region now known to be characterized by a unique vasculature, wherein the drug is relatively contained with a reproductive blood barrier so that effective levels can be achieved throughout the region, but without systemic levels being achieved. Transport across a mucosal surface into an isolated region is the not the same as, nor predictive of, transport through the skin and into the breast.

Differences between the prior art and the claims

Ragavan 1 does not recite all of the limitations of the claims.

Contrary to the formulation disclosed in Ragavan 1, the claimed formulations contain a drug in a pharmaceutically acceptable carrier capable of delivering the drug to the breast tissue in combination with a penetration enhancer, to promote delivery across the skin. Ragavan 1 does not disclose the claimed composition, as acknowledged by the Examiner in withdrawing the rejection of claims 1-4 and 6-9 under 35 U.S.C. §102(b) in view of Ragavan 1.

Ragavan 1 is not concerned with delivery of drugs across the stratum corneum, and does not disclose penetration enhancers to promote delivery of any drug across the stratum corneum. A mere disclosure of triethanolamine or sorbitan esters as an excipient in Ragavan 1, is not tantamount to a disclosure of a penetration enhancer. A reference is considered as a whole. It is

clear that the Examiner is focusing on the obviousness of substitutions and differences, instead of on the invention as a whole. The Supreme Court has made it clear that this is improper.

Nowhere in Ragavan 1 is there mention of a penetration enhancer. Common excipients used in drug formulations have more than a single application-thus the intended use of an excipient is relevant. Oden for example lists gelatin as a binding agent that can be used in solid dosage forms (see Oden, col. 6, line 15) and also lists gelatin as a suspending agent that can be used in liquid formulations (see Oden, col. 6, lines 24-27). The two formulations are different in spite of the fact that they utilize the same excipient. One of ordinary skill in the art will not arrive at the conclusion that that triethanolamine or the sorbitan ester disclosed in Ragavan 1 is effective to enhance penetration across the stratum corneum. However, according to the Examiner, Ragavan 1 employs the same penetration enhancer as required by claim 1, and the same compound cannot have mutually exclusive properties. Applicants respectfully disagree with the Examiner. Ragavan 1 employs the same excipient, which may or may not function as a penetration enhancer. Triethanolamine/sorbitan esters are not invariably penetration enhancers. Triethanolamine can be a ph adjuster or an emulsifier or none of the above, depending on the concentrations employed.

As importantly, the examiner's attention is drawn to the enclosed report. This report demonstrates that one cannot use the formulation described in Ragavan 1 for transdermal delivery. It is completely ineffective.

For at least the reasons discussed above, Applicants submit that the claims are not obvious in view of Ragavan 1.

Double Patenting Rejection

Claims 1-8 were rejected under the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-15 and 31-33 of Ragavan 1, claims 1-4 and 17 of U.S Patent No. 6,652,874 to Ragavan, *et al.* ("Ragavan 2") and claims 1-3 and 12 of U.S. Patent No. 6,416,778 to Ragavan, *et al.* ("Ragavan 3"). Applicants respectfully traverse this rejection for the reasons that are provided above and in view of the accompanying report. Ragavan does not make obvious a method or formulation for transdermal delivery because the formulation disclosed by Ragavan is ineffective in causing transdermal delivery of a drug, danazole..

Legal Standard

When determining whether the claims of an application define an invention that is an obvious variation of an invention defined in the claims of a patent, the claims of the application are compared with the claims in the patent, the disclosure in specification of the patent is not considered in the analysis (*see* MPEP §§ 800-822). The MPEP explains that "[a] double patenting rejection of the obviousness-type is 'analogous to [a failure to meet] the nonobviousness requirement of 35 U.S.C. § 103' except that the patent principally underlying the double patenting rejection is not considered prior art." MPEP § 804(II)(B)(1), citing *In re Braithwaite*, 379 F.2d 594, 154 U.S.P.Q. 29 (CCPA 1967). Therefore, analysis employed in an obviousness-type double patenting rejection parallels the guidelines for a 35 U.S.C. § 103 obviousness determination. *Id.*, citing *In re Braat*, 937 F.2d 589, 19 U.S.P.Q.2d 1289 (Fed. Cir. 1991); *In re Longi*, 759 F.2d 887, 225 U.S.P.Q. 645 (Fed. Cir. 1985).

U.S. Patent No. 9,993,856 to Ragavan, et al. ("Ragavan 1")

Claims 1-9 were rejected under the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-15 and 31-33 of Ragavan 1. This rejection is improper based on a comparison of pending claims 1-9 with claims 1-15 and 31-33 of the Ragavan 1 as shown below.

Claims as Amended	Claims of Ragavan 1
1. A drug formulation comprising a drug selected from the group consisting danazol, bromocriptine, and luteinizing hormone-releasing hormone (LHRH) analogues in an amount effective to provide regional, not systemic, relief from benign diseases or disorders of the breast in a pharmaceutically acceptable carrier selected from the group consisting of a gel, ointment, lotion, emulsion, cream, foam, mousse, liquid, spray, and aerosol capable of delivering the drug to the breast tissue, comprising a penetration enhancer to promote delivery of the drug across the stratum	1. A micro- or nano-particulate drug formulation for local or regional topical administration of an effective amount to provide relief from symptoms associated with a disease or disorder in a region in patients in need thereof, wherein the effective amount is less than the effective amount when the drug is administered systemically. 2. The formulation of claim 1 wherein the region is the female reproductive organs. 3. The formulation of claim 2 wherein the patients have a disorder located in the reproductive organs. 4. The formulation of claim 1 wherein the formulation comprises drug particles. 5. The formulation of claim 3 wherein the drug is

corneum, in a dosage which results in low serum drug levels as compared to the systemic administration of the drug.

2. The drug formulation of claim 1 wherein the drug is soluble in aqueous solutions.

3. The drug formulation of claim 1 wherein the drug is in the form of micro- or nano-particulates.

4. The drug formulation of claim 1 wherein the carrier is a gel.

5. The drug formulation of claim 3, wherein the carrier is a hydroalcoholic gel.

7. The drug formulation of claim 1 wherein the drug is selected from the group consisting of danazol and bromocriptine.

8. The drug formulation of claim 3 wherein the drug is a danazol.

10. A method for treating a disease or disorder of the breast comprising for treatment of endometriosis.

6. The formulation of claim 1 wherein the micro- or nano- particulates adhere to mucosal tissue.

7. The formulation of claim 1 where the micro- or nano- particulates comprise polymer altering rates of drug absorption in the region to be treated.

8. The formulation of claim 1 which can be administered vaginally, intraperitoneally, or directly on the reproductive organs of interest.

9. The formulation of claim 8 wherein the drug is danazol and wherein the formulation is suitable for vaginal administration in patients in need thereof and is in a dosage effective for treatment of endometriosis.

10. The formulation of claim 1 wherein the drug is an anticancer drug, cytotherapeutic or anti-proliferative drug in a dosage effective for treatment of cancer in the region of the patient where administered.

11. The formulation of claim 1 wherein the drug is

topically administering to the breast of a patient,

a drug formulation suitable for local or regional delivery comprising an effective amount of drug selected from the group consisting of danazol, bromocriptine, and luteinizing hormone-releasing hormone (LHRH) analogues to provide regional, not systemic, relief from benign diseases and disorders of the breast,

in a pharmaceutically acceptable carrier selected from the group consisting of a gel, ointment, lotion, emulsion, cream, foam, mousse, liquid, spray, and aerosol capable of delivering the drug to the breast tissue, comprising a penetration enhancer to promote delivery of the drug across the stratum corneum, in a dosage which results in low serum drug levels as compared to the systemic administration of the drug.

an antiviral agent effective for treatment of viral infections selected from genital herpes and genital papilloma viral infections.

12. The formulation of claim 1 wherein the drug is an antifungal agent effective for treatment of vaginal fungal infections.

13. The formulation of claim 1 wherein the drug is an antibacterial agent effective for treatment of vaginal and endometrial bacterial infections.

14. The formulation of claim 1 wherein the drug is a steroid or steroid-like product suitable for treatment of endocrine conditions.

15. The formulation of claim 14 wherein the drug is effective for treatment of menopause, infertility, contraception, dysfunctional uterine bleeding, dysmenorrhea, adenomyosis, or assisted reproductive technologies.

31. A composition for treating endometriosis comprising danazole in a form promoting quick uptake into the blood stream when applied to the

11. The method of claim 10 wherein the drug is in the form of micro- or nano-particulates. 12. The method of claim 10 wherein the carrier is a gel. 14. The method of claim 13 wherein the drug is selected from the group consisting of danazol and bromocriptine. 15. The method of claim 11 wherein the drug is danazol. 17. The method of claim 10 wherein the benign disease of the breast is selected from the group consisting of mastalgia, mastodynia, Mondor's disease, fibrocystic breast disease, costochondritis, mastitis, Paget's disease of the areola, fibroadenoma, breast abscess, and breast infections. 19. The method of claim 10 wherein the region is the breast, areola, and underlying musculature of the chest.	mucosal membranes of the female reproductive tract, wherein danazole is in a form delivering an effective amount to decrease the discomfort of endometriosis which is less than the effective amount when the drug is administered systemically. 32. The composition of claim 31 wherein the danazole is in a form selected from the group consisting of foams, tablets, and creams. 33. The composition of claim 32 wherein the danazole is in a form suitable for application to the uterus.

Independent claim 1 of Ragavan 1 defines a micro- or nano-particulate drug formulation for local or regional topical administration of an effective amount to provide relief from symptoms associated with a disease or disorder in a region in patients in need thereof, wherein the effective amount is less than the effective amount when the drug is administered systemically. Independent claim 31 of Ragavan 1 defines a composition for treating endometriosis comprising danazol in a form promoting quick uptake into the blood stream when applied to the mucosal membranes of the female reproductive tract, wherein danazol is in a form delivering an effective amount to decrease the discomfort of endometriosis which is less than the effective amount when the drug is administered systemically.

None of claims 1-15 and 31-33 of Ragavan 1 defines nor makes obvious a formulation comprising a drug in a pharmaceutically acceptable carrier and penetration enhancer for delivery of an effective amount of the drug to the breast tissue.

None of the claims define a formulation comprising a drug and a penetration enhancer to promote delivery of the drug across the stratum corneum.

There is nothing in the claims of Ragavan 1 that leads one to make a formulation of a drug in combination with a penetration enhancer as claimed.

"Region" as recited in claim 1 of Ragavan 1 is defined as reproductive organs and their surrounding environs - which include uterus, fallopian tube, peritoneal space, pelvic cul-de-sac, ovaries, perineum and the rectovaginal region (*See* Ragavan 1, at least at col. 7, lines 37-41). Thus, Ragavan 1 claims formulations for delivery across mucosal membranes. The Examiner has provided no reasons (*See* MPEP §804) why one of ordinary skill in the art would conclude

that the claimed formulation (i.e. a formulation with excipients that promote delivery across the **skin**, a relatively non-permeable material), is an obvious variation of the formulations claimed in Ragavan 1 (i.e. formulations with excipients for delivery across mucosal membranes). Furthermore, there would be no motivation for one of ordinary skill in the art to modify the formulations claimed in Ragavan 1 to include a penetration enhancer as claimed.

In summary, the claims differ:

In drug to be delivered (for disorders of breast compared to urogenital and reproductive)

In region to be treated (reproductive, highly vascularized mucosal site, compartmentalized via a reproductive blood barrier in women vs. skin on breasts)

Need for excipient (no excipient vs. required to have penetration enhancer – which is determined by difference in properties of region, site of application)

For treatment of different disorders (preferably endometriosis vs. diseases of breast)

Therefore, the claims of the present application are non-obvious over claims 1-15 and 31-33 of Ragavan 1.

U.S Patent No. 6,652,874 to Ragavan, et al. ("Ragavan 2")

Claims 1-9 were rejected under the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4 and 17 of Ragavan 2. This rejection is improper based on a comparison of pending claims 1-9 with claims 1-4 and 17 of the Ragavan 2 as shown below.

Claims as Amended	Claims of Ragavan 2
1. A drug formulation comprising a drug selected from the group consisting danazol, bromocriptine, and luteinizing hormone-releasing hormone (LHRH) analogues in an amount effective to provide regional, not systemic, relief from benign diseases or disorders of the breast in a pharmaceutically acceptable carrier selected from the group consisting of a gel, ointment, lotion, emulsion, cream, foam, mousse, liquid, spray, and aerosol capable of delivering the drug to the breast tissue, comprising a penetration enhancer to promote delivery of the drug across the stratum corneum, in a dosage which results in low serum drug levels as compared to the systemic administration of the drug. 2. The drug formulation of claim 1	1. A drug formulation, comprising drug articles suitable for local or regional administration of an effective amount of the drug to provide relief from symptoms in a region in patients in need thereof, wherein the effective amount is less than the effective amount when the drug is administered systemically and wherein the drug is selected from the group consisting of anticancer drugs, cytotherapeutic drugs, anti-proliferative drugs, and antiviral drugs. 2. The formulation of claim 1 wherein the region is the female reproductive organs. 3. The formulation of claim 2 wherein the patients have a disorder located in the reproductive organs. 4. The formulation of claim 1 wherein the drug is in the form of micro- or nano- particulates. 17. The formulation of claim 1, wherein the

wherein the drug is soluble in aqueous solutions. 3. The drug formulation of claim 1 wherein the drug is in the form of micro- or nano-particulates. 4. The drug formulation of claim 1 wherein the carrier is a gel. 5. The drug formulation of claim 3, wherein the carrier is a hydroalcoholic gel. 7. The drug formulation of claim 1 wherein the drug is selected from the group consisting of danazol and bromocriptine. 8. The drug formulation of claim 3 wherein the drug is a danazol. 10. A method for treating a disease or disorder of the breast comprising topically administering to the breast of a patient, a drug formulation suitable for local or regional delivery comprising an effective	formulation is in a carrier promoting quick uptake of the drug into the blood stream, a carrier manipulating release of drug, or a carrier promoting adhesion of the drug, wherein the carrier is selected from the group consisting of a liquid suspension or dispersion, a hydrogel suspension or dispersion, a topical ointment, a cream, a lotion, and a foam.

amount of drug selected from the group consisting of danazol, bromocriptine, and luteinizing hormone-releasing hormone (LHRH) analogues to provide regional, not systemic, relief from benign diseases and disorders of the breast,

in a pharmaceutically acceptable carrier selected from the group consisting of a gel, ointment, lotion, emulsion, cream, foam, mousse, liquid, spray, and aerosol capable of delivering the drug to the breast tissue, comprising a penetration enhancer to promote delivery of the drug across the stratum corneum, in a dosage which results in low serum drug levels as compared to the systemic administration of the drug.

11. The method of claim 10 wherein the drug is in the form of micro- or nano-particulates.

12. The method of claim 10 wherein

the carrier is a gel. 14. The method of claim 13 wherein the drug is selected from the group consisting of danazol and bromocriptine. 15. The method of claim 11 wherein the drug is danazol. 17. The method of claim 10 wherein the benign disease of the breast is selected from the group consisting of mastalgia, mastodynia, Mondor's disease, fibrocystic breast disease, costochondritis, mastitis, Paget's disease of the areola, fibroadenoma, breast abscess, and breast infections. 19. The method of claim 10 wherein the region is the breast, areola, and underlying musculature of the chest.	

Independent claim 1 of Ragavan 2 defines a drug formulation, comprising drug particles suitable for local or regional administration of an effective amount of the drug to provide relief from symptoms in a region in patients in need thereof, wherein the effective amount is less than the effective amount when the drug is administered systemically and wherein the drug is selected

from the group consisting of anticancer drugs, cytotherapeutic drugs, anti-proliferative drugs, and antiviral drugs.

The same comments and analysis apply as above.

None of the claims 1-4 and 17 of Ragavan 2 defines a formulation comprising a drug in a pharmaceutically acceptable capable of delivering the drug to the breast tissue.

None of the claims define a formulation comprising a drug and a penetration enhancer to promote delivery of the drug across the stratum corneum.

There is nothing in claims 1-4 and 17 of Ragavan 2 that leads one to make a formulation of a drug in combination with a penetration enhancer.

"Region" as recited in claim 1 of Ragavan 2 is defined as reproductive organs and their surrounding environs - which include uterus, fallopian tube, peritoneal space, pelvic cul-de-sac, ovaries, perineum and the rectovaginal region (*See* Ragavan 2, col. 6, lines 32-39). Ragavan 2 claims formulations for delivery across mucosal membranes. The Examiner has provided no reasons (*See* MPEP §804) why one of ordinary skill in the art would conclude that the claimed formulation (i.e. a formulation with excipients that promote delivery across the skin), is an obvious variation of the formulations claimed in Ragavan 2 (i.e. formulations with excipients for delivery across mucosal membranes) when the requirements are so drastically different. Furthermore, there would be no motivation for one of ordinary skill in the art to modify the formulations claimed in Ragavan 2 to include a penetration enhancer as claimed.

Therefore, the claims of the present application are non-obvious over claims 1-4 and 17 of Ragavan 2.

U.S. Patent No. 6,416,778 to Ragavan, et al. ("Ragavan 3")

Claims 1-9 were rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 and 12 of Ragavan 3. This rejection is improper based on a comparison of pending claims 1-9 with claims 1-3 and 12 of the Ragavan 3 as shown below.

Claims as Amended	**Claims of Ragavan 3**
1. A drug formulation comprising a drug selected from the group consisting danazol, bromocriptine, and luteinizing hormone-releasing hormone (LHRH) analogues in an amount effective to provide regional, not systemic, relief from benign diseases or disorders of the breast in a pharmaceutically acceptable carrier selected from the group consisting of a gel, ointment, lotion, emulsion, cream, foam, mousse, liquid, spray, and aerosol capable of delivering the drug to the breast tissue, comprising a penetration enhancer to promote delivery of the drug across the stratum	1. A drug formulation comprising drug particles suitable for regional administration of an effective amount to provide relief from symptoms of a disease or disorder selected from the group consisting of endometriosis, endometrial bacterial infections, cancer, and endocrine conditions in a region in patients in need thereof, wherein the region is selected from the group consisting of the uterus, fallopian tubes, peritoneal space, pelvic cul-de-sac, ovaries, and urinogenital tract, wherein the effective amount is a dosage which results in low serum drug levels and reduced side effects as compared to systemic administration of the

corneum, in a dosage which results in low serum drug levels as compared to the systemic administration of the drug. 2. The drug formulation of claim 1 wherein the drug is soluble in aqueous solutions. 3. The drug formulation of claim 1 wherein the drug is in the form of micro- or nano-particulates. 4. The drug formulation of claim 1 wherein the carrier is a gel. 5. The drug formulation of claim 3, wherein the carrier is a hydroalcoholic gel. 7. The drug formulation of claim 1 wherein the drug is selected from the group consisting of danazol and bromocriptine. 8. The drug formulation of claim 3 wherein the drug is a danazol. 10. A method for treating a disease or disorder of the breast comprising	drug, and wherein the formulation is in a carrier promoting quick uptake of the drug into the blood stream, a carrier manipulating release of drug, or a carrier promoting adhesion of the drug selected from the group consisting of a liquid suspension or dispersion, a hydrogel suspension or dispersion, a topical ointment, a cream, a lotion, and a foam. 2. The formulation of claim 1 wherein the region is the female reproductive organs. 3. The formulation of claim 2 wherein the patients have a disorder located in the reproductive organs. 12. A composition for treating endometriosis comprising particulate danazole in a carrier promoting quick uptake of the drug into the blood stream, a carrier manipulating release of drug, or a carrier promoting adhesion of the drug, when applied to the mucosal membranes

topically administering to the breast of a patient, a drug formulation suitable for local or regional delivery comprising an effective amount of drug selected from the group consisting of danazol, bromocriptine, and luteinizing hormone-releasing hormone (LHRH) analogues to provide regional, not systemic, relief from benign diseases and disorders of the breast, in a pharmaceutically acceptable carrier selected from the group consisting of a gel, ointment, lotion, emulsion, cream, foam, mousse, liquid, spray, and aerosol capable of delivering the drug to the breast tissue, comprising a penetration enhancer to promote delivery of the drug across the stratum corneum, in a dosage which results in low serum drug levels as compared to the systemic administration of the drug.	of the female reproductive tract, wherein the carrier is selected from the group consisting of a liquid suspension or dispersion, a hydrogel suspension or dispersion, a topical ointment, a cream, a lotion, and a foam wherein the dosage of the danazole is effective to reduce the symptoms of endometriosis without causing blood levels of danazole achieved with systemic administration of the danazole.

11. The method of claim 10 wherein the drug is in the form of micro- or nano-particulates. 12. The method of claim 10 wherein the carrier is a gel. 14. The method of claim 13 wherein the drug is selected from the group consisting of danazol and bromocriptine. 15. The method of claim 11 wherein the drug is danazol. 17. The method of claim 10 wherein the benign disease of the breast is selected from the group consisting of mastalgia, mastodynia, Mondor's disease, fibrocystic breast disease, costochondritis, mastitis, Paget's disease of the areola, fibroadenoma, breast abscess, and breast infections. 19. The method of claim 10 wherein the region is the breast, areola, and underlying musculature of the chest.	

Independent claim 1 of Ragavan 3 defines a drug formulation comprising drug particles suitable for regional administration of an effective amount to provide relief from symptoms of a disease or disorder selected from the group consisting of endometriosis, endometrial bacterial infections, cancer, and endocrine conditions in a region in patients in need thereof,

wherein the region is selected from the group consisting of the uterus, fallopian tubes, peritoneal space, pelvic cul-de-sac, ovaries, and urinogenital tract, wherein the effective amount is a dosage which results in low serum drug levels and reduced side effects as compared to systemic administration of the drug, and

wherein the formulation is in a carrier promoting quick uptake of the drug into the blood stream, a carrier manipulating release of drug, or a carrier promoting adhesion of the drug selected from the group consisting of a liquid suspension or dispersion, a hydrogel suspension or dispersion, a topical ointment, a cream, a lotion, and a foam.

Independent claim 12 defines a composition for treating endometriosis comprising danzole and a carrier. Danazole was not known to be useful for the treatment of benign disorders or diseases of the breast at the time this application was filed.

None of claims 1-3 and 12 of Ragavan 3 defines a formulation comprising a drug in a pharmaceutically acceptable carrier capable of delivering the drug to the breast tissue.

None of the claims define a formulation comprising a drug and a penetration enhancer to promote delivery of the drug across the stratum corneum.

There is nothing in the claims of Ragavan 3 that leads one to make a formulation of a drug in combination with a penetration enhancer which enhances transport through the skin since the patent teaches administration to the mucosa.

"Region" as recited in claim 1 of Ragavan 3 is defined as reproductive organs and their surrounding environs - which include uterus, fallopian tube, peritoneal space, pelvic cul-de-sac, ovaries, perineum and the rectovaginal region (*See* Ragavan 3, col. 6, lines 28-34). Thus, Ragavan 3 claims formulations for delivery across mucosal membranes. The Examiner has provided no reasons (*See* MPEP §804) why one of ordinary skill in the art would conclude that the claimed formulation (i.e. a formulation with excipients that promote delivery across the skin), is an obvious variation of the formulations claimed in Ragavan 3 (i.e. formulations with excipients for delivery across mucosal membranes). Furthermore, there would be no motivation for one of ordinary skill in the art to modify the formulations claimed in Ragavan 3 to include a penetration enhancer as claimed.

Therefore, the claims of the present application are non-obvious in view of claims 1-3 and 12 of Ragavan 3.

Withdrawal of the nonstatutory double patenting rejections is respectfully solicited.

Rejoinder and allowance of all claims 1-5, 7, 8, 10, 11, 12, 14, 15, 17 and 19, as amended, is respectfully solicited.

Respectfully submitted,

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